REMARKS

Claims 1-5 are pending in this application. Claim 1 has been amended. Support for the amendment to Claim 1 may be found generally throughout the specification, and specifically within paragraphs [0048]and [0056]. No new matter has been added by virtue of this amendment.

Claim Rejection – 35 USC Sect 103(a)

Claims 1-5 stand rejected under 35 USC 103(a) as being unpatentable over four (4) combined references (Oldenburg et al. in view of the combination of Lambert et al., Mukhopadhyay et al. and Vandenbark et al.). The Examiner basically alleges that it would be obvious to one of ordinary skill in the art to use the polypeptide inhibitors disclosed by Lambert in the method of Oldenburg to facilitate the high level production of purified peptide. The Examiner additionally alleges that one of ordinary skill in the art would next have been motivated to use the inclusion body purification protocols of Mukhopadhyay in the Oldenburg procedure as modified by Lambert. Finally, the Examiner asserts one of ordinary skill in the art would have looked to and used an non-inclusion body art reference (Vandenbark) to somehow attach a C-terminal glycine residue, despite the explicit warning of Oldenburg of its procedure to certain peptides (including those involving the carboxyl terminus). Applicants respectfully traverse and overcome this rejection.

Oldenbury recites a method for the production/expression of a specific recombinant parathyroid (PTH) analog from E. coli using a specified procedure. Applicants respectfully note that Oldenburg explicitly states that its method requires the substitution of methionine residues with non-cleavable residues (as it uses CNBr) to cleave. Oldenburg further limits the applicability of its procedure with regard to other proteins:

> [t]his **method is restricted**, of course, to those peptides which are tolerant of the deletion or replacement of methionine residues. In addition, the peptide will also contain a homoserine or homoserine lactone at the carboxyl-terminus

> which…may also **compromise {the peptide's} bioactivity** and may pose difficulties if a free carboxyl terminus is needed for peptide activity". Pg 283 (emphasis added)

Additionally, as part of its acknowledged limited and restricted method, Oldenburg requires washing the isolation bodies at ph 7.5 and with 100 ml of 10mM Tris-HCl with 100ml of WTEK (100mM KCl), then resuspension in 10 ml of 10% SDS (a detergent) to solubilize and even sonification of the sample "was necessary to solubilize all of the protein". Binding buffer is then added. (See page 281).

Thus, Oldenburg acknowledges the restriction of its process to certain proteins, acknowledges the presence of a homoserine/homoserine lactone which may compromise the bioactivity of the protein and thus would require an additional modification step to obtain the unmodified protein, requires that the washing step at a pH of 7.5, and the finally additionally requires re-suspension in a detergent.

> Applicants' Claim 1, as amended, specifically recites:
>
> A process for the recombinant production of an antifusogenic peptide by expression of a nucleic acid encoding the antifusogenic peptide as a repeat peptide in a microbial host cell to form inclusion bodies which comprise said repeat peptide, comprising the steps of washing the inclusion bodies with 5.5 to 8.0 mol/l of a denaturing agent at a pH value of at or below pH 6.5, solubilizing the washed inclusion bodies at a pH value of at least pH 9 in the absence or detergents or denaturing agents, and cleaving said repeat peptide to obtain said antifusogenic peptide, wherein the antifusogenic peptide contains a glycine at its C-terminus.

Thus, in comparison to Oldenburg, Applicants' method differs in at least four (4) claimed elements. Applicants' procedure involves in contrast:

1) No additional modification step is needed to obtain the unmodified protein (Oldenburg in contrast would require an additional modification step to eliminate the homoserine or homoserine lactone caused by its procedure);

2) A washing step of at or below pH 6.5 (i.e. acidic pH) (Oldenburg in direct contrast requires pH 7.5, i.e. a basic pH)[1];

3) A solubilizing step in the absence or detergents or denaturing agents (Oldenburg in direct contrast requires detergent to solubilize); and

3) A resultant antifusogenic peptide with a glycine at its C-terminus (Oldenburg, as acknowledged by the Examiner, does not even teach nor suggest antifusogenic peptides; Oldenburg's method further results in the presence of the homoserine/homoserine lactone at the carboxyl terminus).

Applicants respectfully submit that Oldenburg teaches away from the claimed invention. Oldenburg teaches a washing step of pH 7.5, teaches the presence of the homoserine/homoserine lactone at the carboxyl terminus, and teaches that an additional modification step would be necessary. Oldenburg also requires re-suspension in a detergent. Finally, and in addition to the above teaching away/required steps of Oldenburg, Oldenburg teaches that its method is restricted and would **not** be applicable to all peptides, specifically those peptides which are not tolerant to the deletion or replacement of methionine residures and those peptides whose bioactivity would be compromised by a homoserine/homoserine lactone at the carboxyl terminus. One of ordinary skill in the art, having read the acknowledged restricted method of Oldenburg, would not therefore be motivated to use the admitted limitations of Oldenburg.

The addition of Lambert et al does not address any of the limitations and deficiencies of Oldenburg. Lambert is silent as to washing steps, solubilizing steps without detegent, carboxyl-terminus residues and modification steps. Therefore Lambert does not remedy any of the missing four (4) claimed elements of Applicants' claimed method that Oldenburg does not teach nor disclose. Thus, the combination of Lambert

[1] The Examiner contends that modifying pH levels is akin to modifying temperature or concentration levels to an optimum level and thus would generally not be considered patentable as such would be a "general condition() of a claim". However, Applicants respectfully point out the pH level taught by Oldenburg is basic, whereas Applicants claimed pH level is acidic. One of ordinary skill in the art would not generally modify or optimize a taught basic pH outside of the range of a basic pH – i.e. change the basic pH to an acidic pH. As Applicants' specification notes [0047], acidic denaturing conditions were found surprisingly not to solubilize the fusion polypeptide to a considerable extent (but did solubilize a lot of other impurities).

with Oldenburg thus does not teach, suggest or motivate one of ordinary skill in the art to arrive at Applicants' claimed invention.

Similarly, the addition of Mukohopadhyay also does not address any of these differences. There is no motivation shown to modify the pH in the washing step of Oldenburg. Furthermore, Mukohopadhyay, like Lambert, is silent as to the presence of carboxyl-terminus resides or modification steps. Finally, with regard to the use of detergents, Mukohopadhyay teaches away from Applicants' claimed method. Indeed, Mukohopadhyay affirmatively teaches that use of detergents for the solubilization of inclusion bodies is common in the art and that one of ordinary skill in the art would be motivated to use detergents for the solubilization of inclusion bodies:

> "Detergents of any form (cationic, anionic and zwitterionic) have been used for the solubilization of inclusion bodies. [...] Thus, detergent just masks certain hydrophobic patches on the protein surface and enhances its solubility." (p. 86)

Thus, the addition of Mukohopadhyay to Oldenburg actually supports (and encourages one of ordinary skill in the art to use) the Oldenburg method of using detergents to solubilize! One of ordinary skill in the art would thus be encouraged by Mukohopadhyay to not change nor modify Oldenburg's teaching of using detergents in the solublization step. The combination of Mukohopadhyay with Lambert with Oldenburg thus does not teach, suggest or motivate one of ordinary skill in the art to arrive at Applicants' claimed invention. Indeed, Mukohopadhyay and Oldenburg, both singularly and in combination, thus affirmatively teach away from Applicants' claimed invention.

Finally, Vandenbark is not directed to the formation of inclusion bodies in E.coli and the solubilization of inclusion bodies. Vandenbark also therefore fails to remedy the teaching away of the combination of Oldenburg, Lambert and Mukohopadhyay. In addition, Vandebark also does not teach removal of the homoserine or homoserine lactone residue at the C-terminus resulting from Oldenburg and thus the combination

would apparently attach the glycine residue onto the homoserine or homoserine lactone residue at the C-terminus (which is not Applicants' claimed method). Thus, even presuming arguendo that one of ordinary skill in the art would be motivated to choose Vandenbark and that somehow the combination of Vandenbark with Oldenburg would even be enabled, the addition of Vandenbark to the combination of Oldenburg, Lambert and Mukohopadhyay still fails to arrive at Applicant's claimed invention.

Conclusion

Therefore, Applicants submit that the combination of Oldenburg, Lambert, Mukohopadhyay and Vandenbark does not teach, suggest or disclose at least two elements of Claim 1: washing at a pH less than or equal to 6.5, and the solubilization without detergents. In addition, the combination of Oldenburg with Lambert with Mukohopadhyay with Vandenbark would require an additional modification step. As such, Applicants respectfully submit that the combination of Oldenburg with Lambert with Mukohopadhyay with Vandenbark would not anticipate, nor render obvious, each and every element and step of Applicants claimed invention. Applicants respectfully request the 103(a) rejection be withdrawn and Claims 1-5, as amended, be hereby placed into condition for allowance.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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